13. (Amended) A method of selectively inducing apoptosis in prostate tissue *in vivo*, comprising administering to a subject a chimeric prostate-homing pro-apoptotic peptide, which comprises a prostate-homing peptide linked to an antimicrobial peptide,

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said chimeric peptide exhibiting selective toxicity to prostate tissue, and

said antimicrobial peptide having low mammalian cell toxicity when not linked to said prostate-homing peptide.

REMARKS

Claims 1 to 22 are pending, with claims 1 to 7 withdrawn from examination as allegedly directed to a non-elected invention. Claims 8 and 13 have been amended, and claims 18 to 22 canceled herein. Thus, upon entry of the present amendment, claims 8 to 17 will be under examination.

Regarding the amendments

The second full paragraph of page 77 of the specification has been amended to specify that a variety of prostate-homing peptides useful in the invention, which were identified by *in vivo* panning using an X_7 library, are reported in Table 5, rather than Table 7. Support for the amendment can be found in the specification, for example, at page 104, lines 8-10, which indicates that additional prostate-homing sequences identified by *in vivo* panning are shown in Table 5.

The preamble of claim 8 has been amended to indicate that the recited antimicrobial peptide, which is linked to a prostate-homing peptide, is directed to "prostate tissue" rather than "prostate cancer." Support for the amendment to claim 8 can be found throughout the specification, for example, at page 74, lines 11-14, which indicates that a prostate-homing peptide can be used to selectively deliver a moiety to "prostate tissue" and at page 106, lines 2-14, which discloses the ability of the SMSIARL (SEQ ID NO: 207) prostate-homing peptide to deliver the pro-apoptotic $_{D}$(KLAKLAK)$_{2}$ peptide to the prostate and cause increased apoptosis in murine prostate tissue as shown in Figure 7. See, also, the brief description of Figure 7, which indicates that normal prostate tissue from a mouse treated with the SMSIARL-GG-$_{D}$(KLAKLAK)$_{2}$ chimeric peptide was stained by TUNEL (page 8, lines 16-20). Delivery of the chimeric peptides of the invention to prostate tissue is useful, for example, for the treatment of a variety of diseases, including benign nodular hyperplasia, through the induction of selective toxicity (page 78, lines 11-19).

The preamble of claim 13 has been amended to recite a method of "selectively inducing apoptosis in prostate tissue *in vivo*." Support for the amendment to claim 13 can be found in the specification, for example, at page 103, lines 25-29, which indicates that the chimeric peptide SMSIARL-GG-$_{D}$(KLAKLAK)$_{2}$ can selectively induce apoptosis in prostate tissue following systemic administration. Support for the amendment to claim 13 also can be found in the specification, for example, at page 74, lines 14-18, which indicates that apoptosis was induced in the

prostate by systemic administration of the SMSIARL-GG-$_D$(KLAKLAK)$_2$ chimeric peptide, while no evidence of apoptosis was observed in non-prostate tissue.

Claims 8 and 13 further have been amended to independent form and to recite the features of base claim 1 except that the recited chimeric peptide is indicated to exhibit "selective" toxicity to prostate tissue. Support for the amendment to "selective toxicity" is found throughout the specification, for example, at page 74, lines 14-18, which indicates that a chimeric peptide of the invention induce apoptosis in mouse prostate following systemic administration, with no evidence of apoptosis in non-prostate tissues, and at page 24, lines 19-21, which indicates that selective toxicity is enhanced cell death in a selected cell type or tissue as compared to a control cell type or tissue.

As set forth above, the amendments to claims 8 and 13 are supported by the specification and do not add new matter. Accordingly, Applicants respectfully request entry of the enclosed amendments.

Attached hereto as Appendix A is a marked up version of the amended claims showing specific text changes made in the enclosed amendment using underlining to indicate text added and bracketing to indicate text deleted.

Regarding informalities in the specification

The Office Action indicates that the specification contains several informalities with regard to Figures 2 and 3 and their respective figure legends and with regard to Tables 5 and 7.

Regarding Figures 2 and 3

The Office Action states that Figure 2 contains seven panels, but that the description in the specification refers only to two panels, a and b. In addition, the Office Action indicates that Figure 3 contains only two panels, but that the description in the specification of this figure refers to four panels, a through d.

Applicants submit that there is an obvious error in the specification and, in particular, that Figures 2 and 3 were inadvertently switched. Thus, the description of Figure 2, which refers to panels a and b, corresponds to the two panels of Figure 3. See, for example, the description of Figure 2A, which refers to a swelling curve (absorbance spectrum) in the presence of calcium (Ca^{2+}) or $_D$(KLAKLAK)$_2$, and Figure 3A, which shows absorbance on the Y axis in the presence of Ca^{2+} or $_D$(KLAKLAK)$_2$. See, also, the description of Figure 2B, which refers to the 32 kDa caspase-3 proform in the presence of $_D$(KLAKLAK)$_2$ or DLSLARLATARLAI (SEQ ID NO: 204), and Figure 3B, which shows detection of the 32 kDa proform of caspase-3 following treatment with $_D$(KLAKLAK)$_2$ or DLSLARLATARLAI (SEQ ID NO: 204).

Similarly, the description of Figures 3a to 3d refers to panels a through d of Figure 2. See, for example, the brief description of Figure 3a, which refers to microscopic analysis, and panel a of Figure 2, which shows microscopic analysis; the brief description of Figure 3b, which refers to hydrolysis measured in cells treated with CNGRC-GG-$_D$(KLAKLAK)$_2$, and panel b of Figure 2, which shows results obtained following treatment with CNGRC-GG-$_D$(KLAKLAK)$_2$; and the brief description of Figures 3c and 3d, which refers to cell viability over time, and panels c and d of Figure 2, which show viability over time.

In response to this rejection, Applicants submit herewith new Figure 2 (Exhibit A), which corresponds to panels a and b of original Figure 3. Applicants further submit herewith new Figure 3 (Exhibit B), which corresponds to panels a to d of Figure 2 as originally filed. Panels e to g of originally filed Figure 2 have been deleted to conform with the figure legend. In view of the above remarks and new Figures, Applicants respectfully request that this objection be withdrawn.

Regarding Tables 5 and 7

As indicated in the Office Action, page 77, lines 25-26, of the specification states that Table 7 shows prostate-homing peptides, but Table 5, at page 104, is the last table in the specification. Applicants submit that reference to Table 7 on page 77 is an obvious error. Page 77 should refer to Table 5 as indicated by the title of Table 5 on page 104, which

reads "Peptides from Phage Recovered from Prostate," and as indicated by the text above the table which specifies that Table 5 contains prostate-homing sequences identified by *in vivo* panning. Applicants have corrected the reference on page 77 by amendment herein and, accordingly, respectfully request that this objection to the specification be withdrawn.

Regarding dependency of claims 8 and 18

Claims 8 and 18 stand objected to as dependent upon non-elected claim 1. This rejection is rendered moot as claim 8 has been amended to independent form and claim 18 has been canceled herein.

Having addressed each of the several grounds for objection to the specification, Applicants request that the obejection to the specification be withdrawn.

Regarding the rejections of claims 8, 9, 13, 14, 18, and 19 under 35 U.S.C. § 112, first paragraph

The rejections of claims 8, 13, and 18 and of claims 9, 14, and 19 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description are respectfully traversed.

The Office Action alleges that the specification discloses only one chimera useful for the purposes stated in the preambles of the claims and that disclosure of a single chimera is not sufficient for the public to recognize that Applicants

were in possession of the full scope of the invention. In particular, the Office Action asserts that only a single chimeric peptide *able to do the purpose stated in the preambles of the instant claims* is disclosed, namely, SMSIARL-GG-$_D$(KLAKLAK)$_2$. In making this assertion, the Office Action refers to the specification at page 106, line 21, to page 107, line 6, and to Figures 7 and 8 with their corresponding figure legends on page 8.

With regard to claims 9, 14, and 19, the Office Action again alleges that the specification only discloses one prostate-homing peptide that selectively homes to prostate tissue, SMSIARL (SEQ ID NO: 207). The Office Action asserts that disclosure of this single species is not sufficient to convey possession of methods of using the entire genus because one cannot predict additional peptides that are functionally equivalent to SEQ ID NO: 207.

As noted above, the claims have been amended. As amended, claim 8 is drawn to a method of directing an antimicrobial peptide *in vivo* to prostate tissue and claim 13 is directed to a method of selectively inducing apoptosis in prostate tissue *in vivo*. Each of the claimed methods recites administration of a chimeric prostate-homing pro-apoptotic peptide which contains a prostate-homing peptide linked to an antimicrobial peptide, where the chimeric peptide exhibits selective toxicity to prostate tissue and where the antimicrobial peptide has low mammalian cell toxicity when not linked to the prostate-homing peptide.

Applicants submit that the specification provides adequate description for the full scope of the invention as now claimed and that one skilled in the art would recognize that Applicants were in possession of a genus of chimeric prostate-homing pro-apoptotic peptides containing a prostate-homing peptide linked to an antimicrobial peptide. In particular, Applicants submit that to show possession of a claimed genus, all that is required is to show that Applicant was in possession of the necessary common attributes or features of elements possessed by members of the genus. Applicants further note that adequacy of the description in the specification must be considered in view of what was known in the art at the time of filing and that description of the invention can be explicit, implicit, or inherent. In the present case, Applicants provide sufficient explicit description of the antimicrobial peptide component, sufficient explicit description of the prostate-homing peptide component, and further description of the chimera as a whole as described further below.

Antimicrobial peptides

The specification provides written description sufficient to describe the full genus of antimicrobial peptides. As set forth in the specification, antimicrobial peptides useful in the invention are characterized as having low mammalian cell toxicity when not linked to a prostate-homing peptide (page 75, lines 1-8), and further are characterized as a naturally occurring or synthetic peptide which has the ability to kill or slow the growth of one or more microbes such as bacteria

(page 14, lines 20-27). In further describing this genus, the specification teaches that antimicrobial peptides useful in the invention include, for example, the naturally occurring gramicidines, magainins, mellitins, defensins and cecropins (page 15, lines 18-26) as well as other amphipathic α-helical peptides and β-strand/sheet-forming peptides (page 15, lines 3-11). As further taught in the specification, amphipathic α-helical peptides useful in the invention generally have an equivalent number of polar and nonpolar residues within an amphipathic domain and a sufficient number of basic residues to give the peptide and overall positive charge at neutral pH (page 18, lines 18-25). In addition, the specification discloses several species of amphipathic α-helical antimicrobial peptides useful in the invention, such as synthetic peptides based on a heptad building block scheme in which repetitive heptads are compared of repeated trimers with an additional residue. As additional examples, the specification discloses $(KLAKLAK)_2$ (SEQ ID NO: 200), $(KLAKKLA)_2$ (SEQ ID NO: 201), $(KAAKKAA)_2$ (SEQ ID NO: 202), and $(KLGKKLG)_3$ (SEQ ID NO: 203) as well as peptides of the general formula $[(X_1X_2X_2)(X_1X_2X_2)X_1]_n$ (SEQ ID NO: 205) or $[(X_1X_2X_2)X_1(X_1X_2X_2)]_n$ (SEQ ID NO: 206), where X_1 is a polar residue, X_2 is a nonpolar residue; and n is 2 or 3, as described, for example, in Javadpour et al. See the specification at page 19, lines 1-15. Thus, the specification discloses numerous exemplary species in addition to describing the common attributes of antimicrobial peptides useful in the invention.

Applicants further submit that the written description in the specification clearly is sufficient for the full genus of antimicrobial peptides in view of what was known in the art at the time of the invention. In particular, the specification incorporates a variety of references describing antimicrobial peptides at, for example, page 9, lines 14-19; page 15, lines 18-27; page 18, lines 1-10; and page 19, lines 15-18. Thus, the specification clearly provides written description for a variety of naturally occurring and synthetic antimicrobial peptides.

In sum, Applicants submit that the specification adequately describes the antimicrobial peptide component of the genus of chimeric prostate-homing pro-apoptotic peptides and its common characteristics and, in addition, provides a representative number of species of such antimicrobial peptides. In view of this description, one skilled in the art would have recognized that the recited chimeric peptides can be prepared using any of the disclosed antimicrobial peptides or others having the same common attributes as disclosed in the specification.

Prostate-homing peptides

Applicants further submit that the specification provides sufficient written description for the full scope of the genus of prostate-homing peptides. The specification discloses common attributes of the peptides by teaching that the selective homing activity of the prostate-homing peptide component is responsible for selective delivery of the chimeric

prostate-homing pro-apoptotic peptide to prostate tissue (page 75, lines 1-8; page 77, 19-22) and further teaching that prostate-homing peptides useful in the invention are peptides which selectively home *in vivo* to prostate tissue as compared to control tissue and generally are characterized by at least a two-fold greater localization to prostatic tissue as compared to control tissue (page 77, lines 10-18). In addition to providing written description for common attributes of prostate-homing peptides, the specification provides written description for individual species of prostate-homing peptides such as SMSIARL (SEQ ID NO: 207), VSFLEYR (SEQ ID NO: 222), and the peptide species shown in Table 5 of the specification (see, for example, page 77, lines 27-30, and page 104). Thus, the specification clearly describes a variety of individual prostate-homing peptide species as well as common functional attributes of prostate-homing peptides useful in the invention. Applicants submit that, in view of this description, it would have been clear to the skilled person that Applicants were in possession of the complete genus of prostate-homing peptides.

Further regarding claims 9, 14 and 19

Applicants further submit that the specification describes the common attributes of the genus of sequences "functionally equivalent" to SMSIARL (SEQ ID NO: 207) as recited in claims 9, 14 and 19 and, therefore, demonstrate to the skilled person that Applicants had possession of the full scope of the claimed invention. As disclosed in the specification, a peptide is functionally equivalent to SEQ ID NO: 207 if it binds

selectively to the endothelium of prostatic blood vessels and functions similarly to SEQ ID NO: 207 in that it binds selectively to the same receptor (page 78, lines 4-10). Using assays routine in the art, functionally equivalent sequences can be identified, for example, with an *in vivo* competition assay for prostate homing; peptides that compete with SMSIARL (SEQ ID NO: 207) for binding to the endothelium of prostatic blood vessels must bind the same receptor and, therefore, are "functionally equivalent." Thus, by describing the necessary common attributes possessed by members of the genus of sequences "functionally equivalent" to SEQ ID NO: 207, Applicants have shown possession of this genus.

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Chimeric peptides

The Office Action implies that the specification must show a working example for each species to prove the species has the activity recited in the preamble of the claims. Applicants respectfully point out that no such requirement exists, and that the only issue with regard to adequacy of written description is whether one skilled in the art would have recognized that Applicants were in possession of the claimed invention at the time of filing.

In the present case, the specification provides sufficient written description for the recited genus of prostate-homing pro-apoptotic chimeric peptides by description of a genus of antimicrobial peptides and a genus of prostate-homing peptide components. In this regard, the specification discloses

a variety of antimicrobial peptides and a variety of prostate-homing peptides useful in the invention as well as their common attributes (see above). Furthermore, as noted above, written description can be implicit rather than explicit. Thus, while the species SMSIARL-GG-$_D$(KLAKLAK)$_2$ is explicitly disclosed in the specification, numerous other species are implicitly disclosed through description of their component peptides and methods for linking those component peptides. The specification discloses, for example, that prostate-homing peptides and antimicrobial peptides useful in the invention can be linked, for example, through a coupling domain such as -GG-, -AA-, or the like (page 22, lines 1-9) and that additional components such as oligopeptide spacers can be included as part of the chimeric peptide, as described, for example, in Fitzpatrick and Garnett, Anticancer Drug Des. 10:1-9 (1995). See the specification at page 66, lines 23-29. In summary, Applicants submit that the specification provides sufficient written description for the full scope of the genus of prostate-homing pro-apoptotic chimeric peptides by description of a genus of antimicrobial peptides and a genus of prostate-homing peptide components.

In view of the above, one of skill in the art would readily recognize that Applicants were in possession of the invention as claimed at the time of filing. Accordingly, Applicants respectfully request reconsideration and removal of the rejections under 35 U.S.C. § 112, first paragraph.

Regarding rejection of claims 8, 9, 13, 14, and 19 under 35 U.S.C. § 112, second paragraph

The rejection of claims 8, 9, 13, 14, and 19 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed.

Claims 8 and 13 stand rejected because the following terms are allegedly indefinite: "selectively internalized by prostate tissue," "low mammalian cell toxicity," and "high toxicity." In particular, the Office Action asserts that the metes and bounds of these terms are not clear.

Regarding the phrase "selectively internalized by prostate tissue"

Applicants submit that the phrase "selectively internalized by prostate tissue," which was used in reference to a chimeric peptide of the invention, is clear and definite to the skilled person. In particular, one skilled in the art, in view of the specification, understands that this phrase means that a chimeric peptide of the invention is characterized by preferential internalization in prostate tissue as compared to control, non-prostate tissue. In this regard, the specification teaches that chimeric peptides of the invention contain a prostate-homing peptide linked to an antimicrobial peptide and that such chimeric peptides are selectively internalized by prostate tissue (page 75, lines 4-6). The specification further teaches that prostate-homing peptides selectively home *in vivo* to

prostate tissue as compared to control tissue (page 77, lines 10-15) and that a chimeric peptide of the invention is selectively delivered to the prostate due to the selective homing activity of the prostate-homing peptide portion of the chimera (page 77, lines 19-22). Thus, the skilled artisan understands that the chimeric peptides of the invention exhibit selective localization to prostate tissue, where they are internalized, resulting in selective internalization of the chimeric peptide in prostate tissue as compared to control tissue. Thus, in view of what is set forth in the specification, the phrase "selectively internalized by prostate tissue" is clear and definite. However, to advance prosecution, claims 8 and 13 have been amended in a manner which does not incorporate this language. Therefore, Applicants submit that this rejection is moot.

Regarding the phrase "low mammalian cell toxicity"

Applicants further submit that the phrase "low mammalian cell toxicity" is clear and definite in view of the specification. The specification teaches that an antimicrobial peptide having "low mammalian cell toxicity" is a peptide that is not lytic to human erythrocytes or that requires concentrations of greater than 100 μM for lytic activity (see page 16, lines 8-12). The specification further teaches that mammalian cell toxicity readily can be assessed using routine assays, for example, lysis of human erythrocytes *in vitro* as described in Javadpour et al. See the specification at page 16, lines 4-8. In view of what is set forth in the specification, the phrase "low mammalian cell toxicity" is clear and definite to the

skilled person. Accordingly, Applicants respectfully request that this ground for rejecting the claims under the second paragraph of 35 U.S.C. § 112 be removed.

Regarding the phrase "high toxicity"

As amended, claims 8 and 13 recite that the chimeric peptide exhibits "selective toxicity to prostate tissue." Applicants submit that the phrase "selective toxicity," as used herein in reference to a chimeric peptide of the invention, is clear and definite in view of the teachings in the specification. As set forth in the specification, "selective toxicity" means enhanced cell death in a selected cell type or tissue as compared to a control cell type or tissue and is generally characterized by at least a two-fold greater extent of cell death in the selected cell type of tissue as compared to a control cell type or tissue (page 24, lines 19-26). The specification further indicates that a chimeric peptide of the invention can selectively induce apoptosis in prostate tissue as compared to non-prostate tissues (page 74, lines 14-18). Thus, in view of what is set forth in the specification, it is clear that the phrase "selective toxicity" means enhanced cell death, such as apoptosis, in prostate tissue as compared to other non-prostate tissues. In view of the above remarks, Applicants submit that claims 8 and 13 are clear and definite and respectfully request that this ground for rejection be removed.

Regarding functionally equivalent sequences

Claims 9, 14, and 19, which relate to a prostate-homing peptide including the sequence SMSIARL (SEQ ID NO: 207) or a functionally equivalent sequence, stand rejected due to an alleged lack of clarity of the term "functionally equivalent sequence." In particular, the Office Action asserts that it is not clear whether this term refers to the function of the SEQ ID NO: 207 peptide recited in the claim or to the function of prostate-homing peptides in general.

The meaning of the term "functionally equivalent sequence" is clear in view of the content of the specification. In particular, one skilled in the art understands that this term refers to a sequence functionally equivalent to SEQ ID NO: 207. As set forth in the specification, the term "functionally equivalent sequence" refers to the sequence SMSIARL (SEQ ID NO: 207) and means a sequence that, like SEQ ID NO: 207, binds selectively to the endothelium of prostatic blood vessels and functions similarly to SEQ ID NO: 207 in that it binds selectively to the same receptor (page 78, lines 4-10). Given what is set forth in the specification, claims 9, 14, and 19 are clear and definite as written. Applicants therefore respectfully request that this ground for rejection under 35 U.S.C. § 112, second paragraph, be removed.

Regarding the term "selective toxicity"

Claim 13 stands rejected because the metes and bounds of the term "selective toxicity" are allegedly unclear. For the reasons set forth above, Applicants submit that the meaning of the term "selective toxicity" is clear to one skilled in the art in view of the content of the specification. Again, the specification indicates that "selective toxicity" is an enhanced cell death in a selected cell type or tissue as compared to a control cell type or tissue (page 24, lines 19-21). In view of the recitation in claim 13 of selective toxicity "in a prostate tissue," it is clear that the selective toxicity refers to enhanced cell death such as in prostate tissue as compared to a control, non-prostate tissue. Thus, in view of the claim language and the specification, claim 13 is clear and definite as written.

Regarding claim 18

Claim 18 stands rejected due to an alleged lack of antecedent basis for the term "said tumor." This rejection is rendered moot by the cancellation of claim 18.

Having addressed each of the grounds for rejection under 35 U.S.C. § 112, second paragraph, Applicants respectfully request reconsideration and withdrawal of this rejection.

Regarding the rejections under 35 U.S.C. § 103

Regarding rejection of claims 8, 13 , and 18

The rejection of claims 8, 13, and 18 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, Javadpour et al., Bessalle et al., and Alvarez-Bravo et al. is respectfully traversed.

Claims 8, 13, and 18 were previously directed to methods of directing an antimicrobial peptide to, inducing selective toxicity in, or treating, prostate cancer. As amended, claim 8 is drawn to a method of directing an antimicrobial peptide to *prostate tissue*, and claim 13 is directed to a method of selectively inducing apoptosis in *prostate tissue*. In view of cancellation of claim 18, the rejection will be addressed as it relates to pending claims 8 and 13.

Applicants submit that claims 8 and 13 are unobvious over the cited references, which relate to the use of peptides that home to tumors and tumor vasculature. Specifically, none of the cited references, alone or in combination, teach or suggest a chimeric prostate-homing pro-apoptotic peptide, which is characterized, in part, by selective homing to prostate tissue. Further, none of the cited references, alone or in combination, teach or suggest selectively inducing apoptosis in prostate tissue using such a chimeric peptide.

Specifically, the Office Action asserts that Arap et al. describe peptides that deliver drugs to the vasculature of specific tumor blood vessels and treatment of mice bearing human breast carcinomas with such peptides. The Office Action further asserts that the peptides described in Arap et al. bind only to molecules found in tumor-associated blood vessels. As noted above, the instant claims do not involve delivery to tumor-associated blood vessels, but rather to prostate tissue, where, as taught in the specification, the chimeric peptides induce selective toxicity. Nothing in Arap et al. teaches or suggests delivery of an antimicrobial peptide to prostate tissue with a chimeric prostate-homing pro-apoptotic peptide or the selective induction of apoptosis in prostate tissue with such a chimeric peptide.

Several secondary references have been combined with Arap et al. In particular, the Fossa et al. abstract is alleged to describe the need for prostate cancer treatments that minimize generalized toxic effects, and WO 90/12866, U.S. Patent No. 5,789,542, and Javadpour et al. are alleged to describe antimicrobial peptides that include or are identical to SEQ ID NO: 200, and to further describe the low mammalian cell toxicity of such peptides. WO 90/12866 is additionally alleged to report that antimicrobial peptides can lyse cancer cells. Again, however, these references, neither alone nor in combination, describe delivery of an antimicrobial peptide to prostate tissue as a chimera via a prostate-homing peptide or the selective induction of apoptosis in prostate tissue with a chimeric peptide

containing an antimicrobial peptide and a prostate-homing peptide.

Other secondary references are cited in the Office Action to show that there may be advantages to using all-D-enantiomers of a peptide. In particular, Bessalle et al. are alleged describe that all-D enantiomers of peptides may possess biological properties similar to those of the respective L-enantiomer and that the D-enantiomers may be resistant to proteolysis. In addition, Alvarez-Bravo et al. are alleged to report that all-D-enantiomers can exhibit greater antimicrobial activity than the corresponding L-enantiomers. However, these references do not provide what is missing in the earlier cited references, namely, a teaching or suggestion of delivery of an antimicrobial peptide to prostate tissue using a chimeric prostate-homing pro-apoptotic peptide or the selective induction of apoptosis in prostate tissue with such a chimeric peptide.

Further, Applicants submit that WO 90/12866 teaches away from the claimed invention. Specifically, WO 90/12866 reports that normal cells, contacted with an antimicrobial peptide as described therein, do not undergo lysis. In contrast, abnormal cells, such as neoplastic cells which have an aberrant cytoskeleton can be lysed by lytic peptides (page 21, lines 19-27). Thus, WO 90/12866, which reports that antimicrobial peptides have lytic activity only against cancer cells, teaches away from the invention, which relates to prostate tissue, including normal tissue. In view of this reference, one of skill in the art would not have been motivated to prepare the

recited chimeric peptides, which have selective toxicity for prostate tissue rather than cancer cells.

In sum, none of the references cited in the Office Action, alone or in combination, teach or suggest delivery of an antimicrobial peptide to prostate tissue or selective induction of apoptosis in prostate tissue using a chimeric prostate-homing pro-apoptotic peptide. Thus, claims 8 and 13 are unobvious over the combination of cited references and Applicants respectfully request reconsideration and removal of the rejection of these claims under 35 U.S.C. § 103.

Regarding rejection of claims 9, 14, and 19

The rejection of claims 9, 14, and 19 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, Javadpour et al., Bessalle et al., and Alvarez-Bravo et al. as applied to claims 8, 13, and 18, and further in view of WO 99/46284, is respectfully traversed.

WO 99/46284 is cited as allegedly describing the prostate-homing sequence of SEQ ID NO: 207 recited in claims 9, 14, and 19. In view of the cancellation of claim 19, this rejection will be addressed as it pertains to pending claims 14 and 19.

With the amendment of independent claim 8, claim 9 is drawn to a method of directing an antimicrobial peptide to *prostate tissue* by administering a chimeric prostate-homing pro-apoptotic peptide that includes a prostate-homing peptide containing SEQ ID NO: 207. Similarly, with the amendment of independent claim 13, claim 14 is directed to method of selectively inducing apoptosis in *prostate tissue* by administering a chimeric prostate-homing pro-apoptotic peptide that includes a prostate-homing peptide containing SEQ ID NO: 207.

As discussed above, none of the references cited in the Office Action in regard to claims 8 and 13, alone or in combination, teach or suggest the claimed invention. Furthermore, the cited reference WO 99/46284 at best describes prostate-homing peptides and conjugates in which a prostate-homing peptide is linked to a moiety (see, for example, page 3, lines 20-22). The moieties described in the reference include therapeutic agents, detectable agents and tags (page 21, lines 22-29). However, neither WO 99/46284 nor any of the cited references teach or suggest chimeric peptides that include an antimicrobial peptide, such as an antimicrobial peptide having an α-helical structure or the sequence $(KLAKLAK)_2$, and a prostate-homing peptide. Absent such a teaching or suggestion, the claimed methods of directing an antimicrobial peptide to prostate tissue or selectively inducing apoptosis in prostate tissue are unobvious over the cited art.

In view of these remarks, Applicants respectfully request reconsideration and removal of the rejection of claims 9, 14, and 19 under 35 U.S.C. § 103.

Regarding rejection of claims 10, 15, and 20

The rejection of claims 10, 15, and 20 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, Javadpour et al., Bessalle et al., and Alvarez-Bravo et al. as applied to claims 8, 13, and 18 above, and further in view of Ellerby et al., is respectfully traversed.

Claims 10, 15, and 20 are directed to the use of a chimeric peptide containing a specific antimicrobial peptide, which is an all-D enantiomer, $_{D}(KLAKLAK)_{2}$ (SEQ ID NO: 200). Ellerby et al. is cited as allegedly describing a peptide having the same sequence as that of SEQ ID NO: 200. The Office Action further asserts that Bessalle et al. and Alvarez-Bravo et al. describe possible advantages of all-D-enantiomers and concludes that it would have been obvious to use an all-D enantiomer for the treatment of prostate cancer.

With the amendment of independent claim 8, claim 10 is drawn to a method of directing an antimicrobial peptide to prostate tissue by administering a chimeric prostate-homing pro-apoptotic peptide that includes an antimicrobial peptide containing the sequence $_{D}(KLAKLAK)_{2}$. With amendment of independent claim 13, claim 15 is directed to method of

selectively inducing apoptosis in prostate tissue by administering a chimeric prostate-homing pro-apoptotic peptide that includes an antimicrobial peptide containing the sequence $_D(KLAKLAK)_2$. Thus, each of these claims is directed to the use of a chimeric peptide in which a prostate-homing peptide is linked to an antimicrobial peptide.

As discussed above, none of the references cited in the Office Action in regard to claims 8 and 13, alone or in combination, teach or suggest chimeric prostate-homing pro-apoptotic peptides which include a prostate-homing peptide and an anti-microbial peptide. Ellerby et al., the only additionally cited reference, also does not teach or suggest delivery of an antimicrobial peptide to prostate tissue using a chimeric prostate-homing pro-apoptotic peptide or the selective induction of apoptosis in prostate tissue with such a chimeric peptide. At best, Ellerby et al. describe tumor-homing peptides that contain two functional domains. One of these domains is a short *tumor-homing peptide*, such as CNGRC or RGD-4C and the other is a programmed cell death-inducing sequence (see page 1032, abstract and column 2, last paragraph). Ellerby et al. further indicate that these peptides selectively target *angiogenic endothelial cells* (page 1032, column 1, first paragraph) and, in particular, report that the CNGRC-GG-$_D(KLAKLAK)_2$ peptide kills angiogenic but not angiostatic cells (page 1033, column 2, last paragraph and Table 1). The results described by Ellerby et al. are supported by Arap et al., which indicates that endothelial cells in angiogenic vessels within tumors express proteins which are absent or barely detectable in established vessels and that

tumor-homing peptides, such as CNGRC and RGD-4C, may home to such vascular addresses (page 377, column 1, first two paragraphs). Thus, the cited art reports peptides with two functional domains, where one domain targets angiogenic vasculature in preference to angiostatic vasculature. The cited art does not teach or suggest chimeric prostate-homing pro-apoptotic peptides that include, in part, a prostate-homing peptide, nor provide any motivation for making such a chimeric peptide. Absent this, the claimed invention is unobvious over the combination of cited references. In view of these remarks, Applicants respectfully request reconsideration and removal of the rejection of claims 10, 15, and 20 under 35 U.S.C. § 103.

Regarding rejection of claims 11, 12, 16, 17, 21, and 22

The rejection of claims 11, 12, 16, 17, 21, and 22 under 35 U.S.C. § 103 as allegedly unpatentable over the combination of WO 99/46284 and Ellerby et al. as applied to claims 9, 14, and 19 in view of Arap et al., Fossa et al., U.S. Patent No. 5,789,542, WO 90/12866, and Javadpour et al. is respectfully traversed.

The Office Action states that claims 11, 12, 16, 17, 21, and 22 relate to the use of a specific chimeric peptide of the invention. Further, the Office Action alleges that WO 99/46284 describes the prostate-homing part of the chimeric peptide and that Ellerby et al. describes the cancer-killing portion of the chimeric peptide, $_{D}(KLAKLAK)_{2}$, as well as the coupling domain, GG. The Office Action also alleges that the

other references describe why it would have been obvious to one having ordinary skill in the art to make such a chimera to treat prostate cancer. In view of the cancellation of claims 21 and 22, the rejection will be addressed with regard to pending claims 11, 12, 16, and 17.

As noted above, none of the claims currently pending in the application are directed to the treatment of cancer. Rather, amended claims 11 and 12 are drawn to a method of directing an antimicrobial peptide to prostate tissue, where the recited chimeric peptide is SMSIARL-GG-$_D$(KLAKLAK)$_2$ or a peptide containing this sequence. Similarly, amended claims 16 and 17 are directed to a method of selectively inducing apoptosis in prostate tissue, where the recited chimeric peptide is SMSIARL-GG-$_D$(KLAKLAK)$_2$ or a peptide containing this sequence.

Applicants respectfully disagree with the allegation that it would have been obvious to combine the prostate-homing peptide of WO 99/46284 with the antimicrobial peptide, $_D$(KLAKLAK)$_2$ of Ellerby et al. using the -GG- linker described in Ellerby et al. As noted above, Ellerby et al. report that peptides containing $_D$(KLAKLAK)$_2$ kill angiogenic but not angiostatic cells (page 1033, column 2, last paragraph). Additionally, WO 90/12866 describes differences in the activity of antimicrobial lytic peptides on normal and abnormal, or cancerous, cells. In particular, WO 90/12866 reports that their lytic peptides, while effective in lysing abnormal cells such as cancer cells, do not lyse normal cells. Given what was known in the art at the time of the invention, one of ordinary skill in

the art would not have been motivated to make a chimeric pro-apoptotic peptide that includes a prostate-homing peptide and an antimicrobial peptide such as $_D(KLAKLAK)_2$ or to administer such a chimeric peptide so that it would be directed *in vivo* to prostate tissue, or would selectively induce toxicity in prostate tissue *in vivo*. Absent such a motivation, the claimed invention is unobvious over the combination of cited references.

In view of these remarks, Applicants respectfully request reconsideration and removal of the rejection of claims 11, 12, 16, 17, 21, and 22 under 35 U.S.C. § 103.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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Date

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